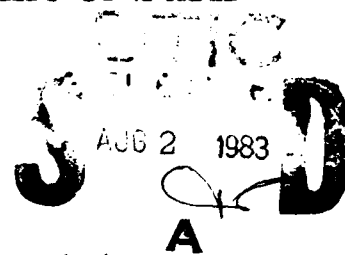


Hypermetabolic low triiodothyronine syndrome of burn injury

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The free tetraiodothyronine index (FT₄I) and free triiodothyronine index (FT₃I) in burn patients represented the serum levels of free (dialyzable) T₄ and free T₃, respectively. FT₄I and FT₃I were lower with greater burn size and were lower in nonsurvivors than expected for the burn size. There was no compensatory elevation of basal or releasing hormone-stimulated thyrotrophin (TSH) concentrations. Reverse T₃ was higher with greater burn size. T₃ treatment restored FT₃I but did not affect mortality or resting metabolic rate (MR) measured in survivors, compared with placebo therapy. Whereas the hypermetabolic response to burn injury appeared to be independent of thyroid hormones, MR was correlated positively with burn size and with elevated plasma nor-epinephrine and epinephrine concentrations for several weeks after injury. Lack of augmented TSH concentrations, absence of low plasma reverse T₃, and presence of hypermetabolism suggest that the reduced plasma free T₃ does not indicate functional hypothyroidism, but may represent an adaptation to the assumption of metabolic control by the sympathetic nervous system.

Many nonthyroidal illnesses (NTI), such as starvation, infection, liver disease,^{1,2} kidney disease,³ malignancy,⁴ myocardial infarction,⁵ diabetes mellitus,⁶ and accidental burn injury^{7,8} are associated with a decrease in total and free T₄ concentration in plasma (low T₄ syndrome). Reduction in T₄ may signify a more critical severity of illness: among patients admitted to a medical intensive care facility, those with a low total T₄ had a subsequent mortality (63%) of more than 4-fold that of patients with normal T₄.⁹ In the same¹⁰ and in another¹¹ medical ICU, patients with a reduced T₄ level also had a dramatically reduced free (dialyzable) T₄ concentration and FT₄I compared to patients with normal T₄¹⁰ or to normal controls.¹¹

A major unresolved issue is whether this chemical hypothyroidism of illness and trauma represents functional hypothyroidism requiring replacement therapy.

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Alternatively, it could represent an adaptive response. Such a response might serve to lower MR at a time when normal oxygen demand and catabolic activity could presumably be disadvantageous, or it might occur without lowering of MR if another system assumes the dominant role in stimulating MR. Previous studies of burns or other NTI have not examined concentrations of thyroid hormones and catecholamines in plasma with respect to the extent of illness or injury or to metabolic rate. However, patients with injury from burns¹² or other trauma¹³ or with several kinds of febrile illnesses¹⁴ have been hypermetabolic, an association unexpected with hypothyroidism. Accidental burn injury in which severity of insult to the patient can be quantitated as burn size provides a model in which the hormonal and metabolic variables can be explored in relationship to each other and to time after injury and extent of injury. We have assessed the pituitary-thyroid axis using thyrotrophin-releasing hormone (TRH) and have examined the interrelationship among thyroid hormones, catecholamines, and metabolic rate in patients recovering from burn injuries of varying extent, with or without T₃ replacement.

PATIENTS AND METHODS

Study 1

Five nonburned healthy controls (CONT) and 10 burn patients received a single 250 µg iv bolus of thyrotrophin-releasing hormone (TRH) between postburn days (PBD) 10 and 20. Five burn patients survived (SURV) and 5 nonsurvivors (NSURV) expired later (Table 1). No patient received dopamine or corticosteroids before or during TRH stimulation. Serum samples were taken for TSH assay before and at intervals up to 90 min after TRH injection. The TSH-time curve integral (area under the curve) was computed. Analysis of variance and the Student-Newman-Keuls test were used to compare means.

Study 2

Thirty-six men, aged 17-23 yr and burned in a single gasoline fire in a military camp, were entered into a prospective study of T₃ versus placebo administration on a protocol approved by the institutional committee monitoring ethical considerations of clinical studies. Eight of

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TABLE 1. Basal FT₄I and FT₄I and TRH-stimulated TSH response in normal and burned subjects

Group	Age (yr)	N/Sex	TBS range (mean) ^a	Days before death	FT ₄ I	FT ₄ I	TSH Integral (U·min/ml)
CONT	31-40	5/M			7.9 ± 0.35	153 ± 9.5	1245 ± 208
SURV	19-54	5/M	50-68 (58)		5.9 ± 0.7 ^b	95.0 ± 21.0 ^c	1326 ± 216
NSURV	18-63	4/M 1/F	28-68 (47)	4-7	2.9 ± 0.6 ^c	25.0 ± 6.0 ^c	579 ± 109 ^c

^a TBS, total burn size as % body surface; for group designations, see Figure 2.

^b $p < 0.05$; ^c $p < 0.01$; for SURV, comparison group is CONT; for NSURV, comparison group is SURV. Error terms are SEM.

these CONT patients had minimal injury. The remaining 28 had 2nd and 3rd degree total burn size (TBS) of 18-93% of body surface area and were randomly assigned in double blind fashion to treatment with either placebo or T₃ 200 µg/day orally or by nasogastric tube in 4 divided doses until their wounds were healed. This dose of T₃ was previously found to maintain normal T₃ levels in burn patients.¹⁵ Because 4 deaths occurred during placebo (NSURV) and 4 during T₃ treatment (NSURV-TX), the patients were assessed according to the 5 groups characterized in Table 2. We sampled blood for determination of thyroid hormones (serum) and catecholamines (plasma) beginning on PBD 3-5, and then approximately thrice weekly, when the patients were under basal conditions in the supine position between 0500-0700 h, just before their next dose of placebo or T₃. At weekly intervals in the morning, after overnight recumbency and at least an 8-h period free of caloric intake, resting MR was measured in all surviving patients. Because of the large number of measurements to be made, priority was given to those who appeared the most stable clinically, and their MR was followed longitudinally. The others, whose MR was not measured, happened to be nonsurvivors. A record was kept of the total daily caloric intake and the separate intakes of carbohydrate, protein and fat.

In Study 2, the period of PBD 3-26 was chosen for analysis, because the major decrement in catecholamines and MR occurred by PBD 26, the CONT patients were available for varying periods up to this time, and all survivors received placebo or T₃ treatment during this time (Table 2). All values sampled within 24 h of dopamine or corticosteroid administration were discarded from analysis. In one analysis the variables were considered as the mean value for each patient. But, because major changes in most variables took place over time, the time factor was accounted in separate analyses using individual values of variables in a standard stepwise multiple linear regression program (BMDP, UCLA) performed on a PDP 1140 computer. For a given dependent variable, the program chose only those independent variables (from the ones entered) which significantly ($p < 0.05$) reduced the residual variance of the dependent variable about the values predicted from the other chosen independent variables. To test for possible dependent

TABLE 2. Group characteristics of the T₃ treatment study^a

	N	%TBS (mean)	%TBS (range)	Begin placebo or T ₃ (PBD)	End placebo or T ₃ (PBD)
CONT	8	4.5	2-7.5		
SURV	10	44.3	18-82	3	31-104
NSURV	4	68.4	55-93	3	6-54
SURV-TX	10	45.3	28-75	3	26-83
NSURV-TX	4	72.9	62-85	3	12-22

^a TBS, total burn size as % body surface; PBD, postburn day; CONT, controls with small burns; SURV, placebo-treated survivors; NSURV, placebo-treated nonsurvivors; SURV-TX, T₃-treated survivors; NSURV-TX, T₃-treated nonsurvivors.

variation related to TBS and PBD, both of these and their respective squared values were entered as possible independent variables into most of the multiple regression analyses. Additional possible independent variables were also entered to determine whether they would account for dependent variation better than would TBS and PBD. In some analyses, death or T₃ treatment was entered as the additional independent variable. In other analyses involving several hormones as the additional possible independent variables, the relevant dependent and independent variables are identified under "Results" and in Table 3.

In both of these studies (1 and 2), no patient received iodine or iodine-containing compounds topically or systemically. All patients received initial vigorous fluid resuscitation followed by administration of calories, mainly by the enteral route, to approach the estimated metabolic requirement. Wounds were treated with open topical applications of mafenide acetate or silver sulfadiazine and excision and grafting when appropriate. Systemic antibiotics were administered for sepsis or infection.

Assays

Determinations of T₄, T₃ (Ortho), reverse T₃ (rT₃, Serono) and TSH (Diagnostic Products) were made by radioimmunoassays with kits obtained from the manufacturer. Least detectable concentrations were 0.2 µg/dl for T₄, 10 ng/dl for T₃, 2 ng/dl for rT₃, and 0.5 µU/ml for TSH. Pooled hypothyroid, normal, and hyperthyroid sera yielded respective mean values (and interassay coefficients of variation) as follows: for T₄, 4.7 (7.4%), 9.5 (7.1%), and 17.1 µg/dl (7.6%); for T₃, 60 (8.3%), 124

TABLE 3. Regression analyses of hormonal variables and MR

Analysis ^a	n	r ²
$FT_4I^b = 7.34 - 0.0003 TBS^2 - 0.002 DA + 0.001 PBD^2$	143	0.344
$FT_3I^b = 98.6 - 0.568 TBS + 0.046 PBD^2 - 0.035 DA$	143	0.417
$rT_3^b = 44.2 - 3.75 PBD + 0.094 PBD^2 + 0.255 TBS - 0.002 TBS^2$	143	0.540
$TSH = 1.69 + 0.085 PBD$	141	0.129
$NE^c = 1425 + 22.7 TBS - 122 PBD - 0.186 TBS^2 + 2.92 PBD^2 - 58.2 FT_4I$	142	0.639
$EPI^c = 143 + 3.0 TBS - 8.75 PBD$	142	0.397
$DA^c = 208 + 0.026 TBS^2 - 1.23 FT_3I$	142	0.290
$DBH/P^c = 90.1 - 0.306 FT_4I$	141	0.037
$MR = 35.1 + 0.243 TBS + 0.017 NE - 1.74 TSH + 0.041 DBH/P$	36	0.827
$MR^d = 35.2 + 0.022 NE + 0.036 EPI$	37	0.576

^a In each analysis, all variables (except MR) were entered, together with TBS and PBD and their squared values, as possible independent variables with the following exceptions:

^b If a thyroid hormone (FT_4I , FT_3I or rT_3) was the dependent variable, none of these was entered as an independent variable.

^c If a catecholamine-related measurement was the dependent variable (NE, EPI, DA, or DBH/P), none of these was entered as an independent variable.

^d In this analysis, only NE, EPI, and DA were entered as possible independent variables. The proportion of MR variability (r^2) associated with NE alone was 0.50, and the inclusion of EPI accounted for an additional 0.076.

(3.3%), and 298 ng/dl (4.48%); and for TSH, 36.4 (9.1%), 3.3 (10.7%), and 1.5 μ U/ml (35%). For rT_3 , pooled hypothyroid and normal sera yielded respective means (and interassay coefficients of variation) of 11.8 (8.3%) and 22.3 ng/dl (13.9%). Indices of free thyroid hormone concentration (FT_4I and FT_3I) were calculated as the product of the total T_4 or T_3 and the resin T_3 uptake (T_3U) divided by the normal calibrator T_3U provided in the kit (Ortho). The FT_4I and FT_3I in 100 representative samples from burn patients (Fig. 1) were validated as indices of free hormone levels by comparison with the respective free T_4 and free T_3 concentration based on the dialyzable fraction which was also determined (Nichols Institute, San Pedro, CA). These samples were taken from patients with various burn sizes, including some with nearly healed wounds and normal thyroid hormone levels. In a group of 49 normal adults, mean FT_4I was 7.48 (range 5.1–11.1) and mean FT_3I was 125 (range 69–273). These index values have no assigned units. Plasma norepinephrine (NE), epinephrine (EPI) and dopamine (DA) were determined by radioenzymatic assay¹⁶ as was dopamine beta-hydroxylase (DBH).¹⁷ Total plasma protein was determined according to the method of Lowry et al.¹⁸ Resting MR was measured at ambient 31°C by indirect calorimetry based on O_2 consumption measured for successive 2-min intervals using a head canopy with continuous air flow.¹⁹ The lowest value for a 30-min period, usually when the patient was asleep, was taken for the MR measurement.

RESULTS

Figure 1 shows the comparison of FT_4I and FT_3I with the free hormone levels by dialysis (FT_4 and FT_3 , respectively) in 100 representative samples from burn patients. The close correlations indicate that low FT_4 and FT_3 are associated with proportionately low FT_4I and FT_3I , respectively.

In Study 1 (Table 1 and Fig. 2), TRH stimulation in SURV did not produce an exaggerated TSH response, though 4 out of 5 had basal FT_3I below the lowest value for healthy controls. The response was blunted and delayed in NSURV, whose TSH concentration was higher at 60 than at 30 min after injection in every case. In contrast, TSH was lower at 60 than at 30 min after TRH injection in all CONT and SURV.

In Study 2, 4 of 14 T_3 -treated and 4 of 14 placebo-treated patients died with sepsis or pneumonia. There were a total of 16 patients with TBS > 50% (to include

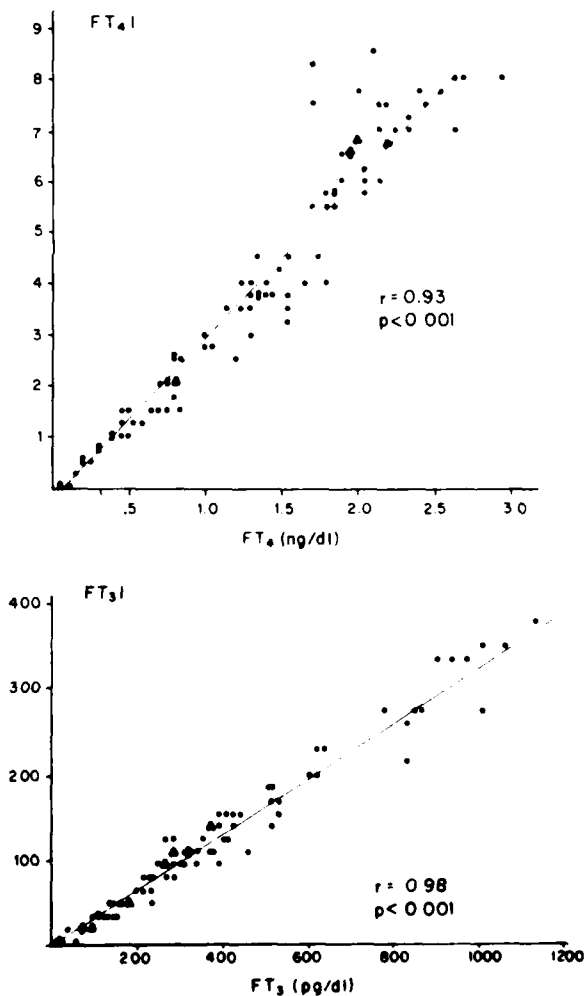


FIG. 1. Correlation of FT_4I and FT_3I with respective free hormone concentrations derived from the dialyzable fraction.

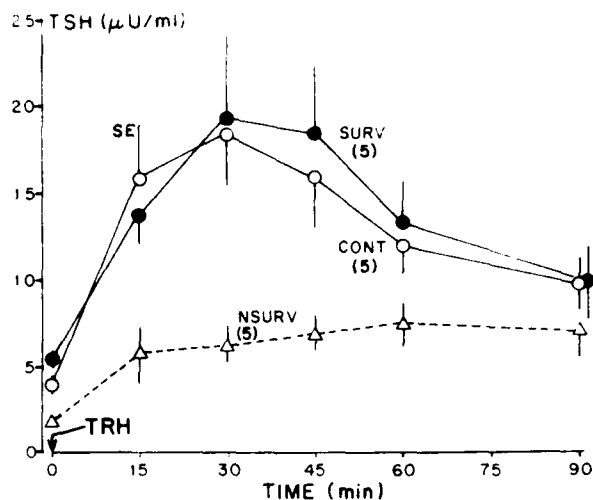


FIG. 2. TSH response to TRH in surviving (SURV) and nonsurviving (NSURV) burn patients and nonburned healthy controls (CONT). The number of patients is indicated in parentheses.

all nonsurvivors), in which 4 of 8 T_3 -treated and 4 of 8 placebo-treated patients died. The CONT group with a very small injury (Table 2) known not to influence MR¹² consisted of particularly appropriate control subjects for this study. They were homogeneous with the other patients with respect to age, sex, physical training, and previous environment, and they were housed in the same general ward area. Therefore, hormonal values for the more extensively burned patients are better compared to values for these controls rather than to normal ranges in a heterogeneous population.

FT_4I and FT_3I in SURV were lowest initially (PBD 3-5) and generally returned to CONT levels over 3-4 weeks. In NSURV, the values were initially lower and did not rise before death which occurred on PBD 6-54. On PBD 5 (CONT samples not taken earlier), FT_4I (mean \pm SE) in SURV was slightly but not significantly lower (6.59 ± 0.46) than in CONT (7.62 ± 0.42), and FT_3I in SURV (63.6 ± 3.9) was lower ($p < 0.001$, Student's *t*-test) than in CONT (99.8 ± 4.5). On PBD 3, FT_4I in NSURV was 3.57 ± 0.63 compared to 7.11 ± 0.62 in SURV ($p < 0.01$) and FT_3I in NSURV was 26.5 ± 7.38 compared to 69.8 ± 12.1 in SURV ($p < 0.001$). Because both time since burn and burn size were important variables, hormonal values in relation to burn size were first considered as the mean value for each patient over PBD 3-26. Subsequently, individual values were analyzed over this time period with PBD and TBS as independent variables in multiple regression analyses. Because of variation with time and less variation of FT_4I than FT_3I with burn size, only the multiple regression approach, accounting for time since burn, showed a significant burn size-related suppression of FT_4I in SURV.

Based on mean values for each patient, the reduction

in FT_3I was proportional to burn size in patients not treated with T_3 (Fig. 3, upper left). Comparison of mean FT_4I and TSH suggests that the thyroid axis was similarly suppressed in NSURV and in T_3 -treated patients (Fig. 3, upper right). An inverse relationship between rT_3 and FT_4I or FT_3I can also be seen in patients not treated with T_3 (Fig. 3, lower panels). Multiple regression analyses showed that T_4 , T_3 , FT_4I , and FT_3I ($p < 0.001$) were inversely proportional to TBS or TBS² in placebo-treated patients. In these patients, T_4 , T_3 , FT_4I , FT_3I , and TSH were excessively low ($p < 0.01$) for burn size in the NSURV group. T_3 treatment raised T_3 and FT_3I in SURV-TX and NSURV-TX ($p < 0.001$) and suppressed T_4 , FT_4I , and TSH ($p < 0.001$) in survivors but not in nonsurvivors. Figure 3 (right panels) shows the corresponding results based on mean values for each patient for FT_4I , TSH, and FT_3I . Multiple regression analysis showed that in placebo-treated patients, higher rT_3 was associated with greater TBS ($p < 0.01$). T_3 treatment reduced rT_3 in SURV-TX ($p < 0.001$) but not in NSURV-TX patients (Fig. 3, lower panels).

Patients with more extensive burns had higher NE levels and MR, particularly in the first 3 weeks postinjury, and MR was positively correlated with NE (Fig. 4). NE and MR were both inversely correlated with FT_3I ($p < 0.001$, not shown) in placebo-treated patients. Multiple regression analysis showed that EPI ($p < 0.001$) and DA ($p < 0.01$) were also elevated in proportion to TBS and that NSURV had elevated plasma DA ($p < 0.01$) but not NE or EPI concentrations out of proportion

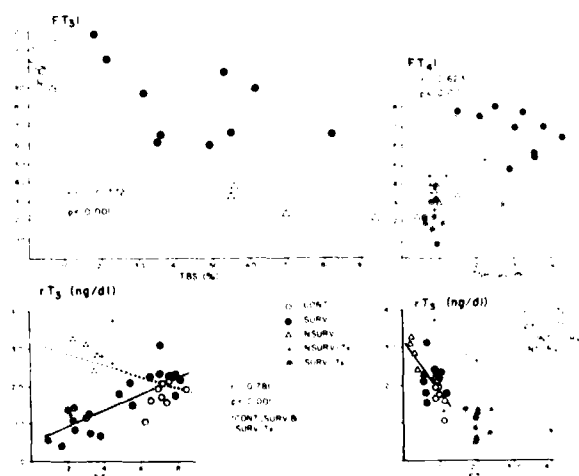


FIG. 3. Relationships among thyroid hormones, TBS, and TSH based on linear correlations of mean hormone values for each patient over PBD 3-26. In the upper right panel, location nearer the origin indicates suppression of the pituitary-thyroid axis, and the dashed line completely separates CONT and placebo-treated SURV from the others nearer the origin. The shaded areas (lower panels) include at least all points in the regressions for groups specified in the figure. In the lower left panel, the regression depicted (solid line) is positive, because nonsurvivors are excluded. If only T_3 -treated patients are excluded, then the relationship between rT_3 and FT_4I (dotted line) is negative ($r = -0.49$, $p < 0.05$).

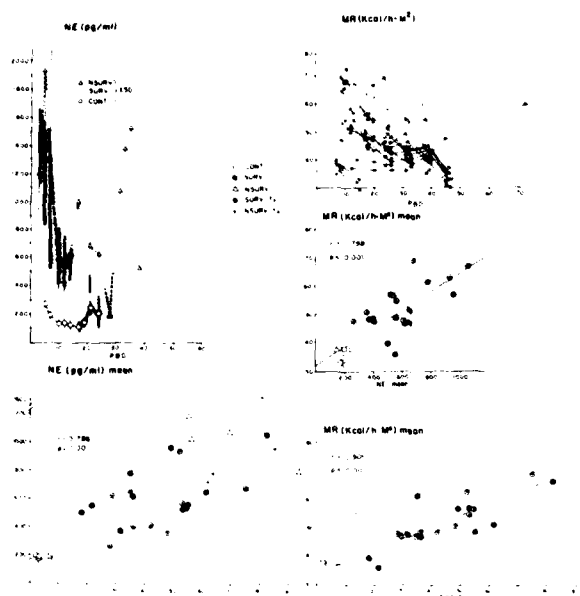


FIG. 4. Elevated NE and MR in burn patients related to PBD and TBS. Linear correlations are based on mean values over PBD 3-26. For group designations, see Table 2.

to TBS. Although SURV-TX had slightly lower NE values than did placebo-treated SURV for any given TBS and PBD ($p < 0.05$), NE levels were still markedly elevated in SURV-TX ($p < 0.001$). There was no detectable effect of T_4 treatment on EPI, DA, or MR.

Interrelationships among the measured values in untreated patients were defined by considering FT_4I , FT_3I , rT_3 , TSH, NE, EPI, DA, DBH corrected for total serum protein (DBH/P), or MR as the dependent variable in separate multiple regression analyses. The remaining hormones (except those noted in Table 3) were entered together with TBS and PBD as possible independent variables. The resultant computer-chosen independent variables (Table 3) indicate that TSH has no correlation with thyroid hormones; thyroid hormones and catecholamines vary with burn size and time since the burn, and NE is inversely related to FT_4I . MR was more closely related to NE than to EPI, in that the latter was not chosen as a predictor for MR from among the other variables. When TBS, PBD, and thyroid measurements were excluded from analysis, NE accounted for 50% of total MR variability, and inclusion of EPI accounted for another 7.6%. In analyses not shown, FT_4I , FT_3I , NE, and MR were not correlated with total or fractionated caloric intake among SURV, indicating that differences in nutrition did not influence the metabolic variables estimated in these patients. However, the mean total caloric intake for individual nonsurvivors was lower (NSURV, 609-1354; NSURV-TX, 537-1522 kcal/M²·day) than for survivors (SURV, 1526-2192; SURV-TX, 1630-2256 kcal/M²·day).

DISCUSSION

In agreement with previous findings,^{7,8,15} we have confirmed that severe burns suppress free indices of thyroid hormone levels. Additionally, we now show that this is related to extent of injury and is without an augmentation of TRH-stimulated plasma TSH. An augmented TSH response is the expected normal result of even smaller decrements in thyroid hormones.²⁰ NSURV of burns had the lowest FT_4I and FT_3I and also exhibited a blunted and delayed TSH response to TRH. The altered regulation of TSH in burn patients resembles that found in other forms of NTI.^{3,4} These results are compatible with failure of brain centers controlling the thyroid axis²¹ or with direct suppression of TSH release by elevated DA²² or cortisol.^{23,24} Whether the excessively low FT_4I , FT_3I and TSH values for NSURV burn patients are a result of sepsis, a deficient caloric intake, or other factors is yet to be determined. Though some unidentified factor also might interfere with hormone release from the thyroid, the thyroids from our patients at autopsy microscopically indicate lack of TSH stimulation.

Inhibited peripheral conversion of T_4 to T_3 and accumulation of the inactive rT_3 (the product of inner ring monodeiodination of T_4 in the periphery) are features of other forms of NTI.^{1,2,6} Similarly, we found an inverse relationship of rT_3 to FT_4I in burn patients not treated with T_4 . The presence of normal or high rT_3 may be evidence for lack of hypothyroidism in burn injury, in that such levels of rT_3 have also been used to distinguish other forms of NTI from classical hypothyroidism.²⁵

Burned patients are hypermetabolic, which again suggests the absence of functional hypothyroidism. Their hypermetabolism is blunted by propranolol,¹² a β -blocker. Their urinary catecholamines are elevated^{12,26,27} in proportion to MR^{12,27} as are their plasma catecholamines as shown in the present study. MR was more closely correlated with NE than EPI, suggesting β_1 mediation of some of the hypermetabolism. Another study failed to find a correlation between plasma catecholamines and MR in children whose hypermetabolism and catecholamine levels were partially reduced by restricting heat loss with occlusive dressings.²⁸ Reduction in metabolic and sympathetic signals together with fewer measurements may have reduced the chance to observe a correlation in that study. Burn patients also exhibit other signs of elevated sympathetic activity,^{12,15,27} such as elevation of heart rate, cardiac output and core temperature. In our placebo-treated patients, larger burn size and lower FT_4I were closely correlated with higher plasma NE and higher MR, and MR was inversely related to plasma TSH. Thus, downward adjustment of TSH secretion appears not to indicate central hypothyroidism but perhaps is a response to the metabolic effect of catecholamines. T_4 treatment did not alter mortality in

this study. Failure of T_3 replacement to alter the MR further indicates that the hypermetabolic response to injury is independent of stimulation by the thyroid axis. The fall in thyroid hormones may be an adaptation to the assumption of metabolic control by the sympathetic nervous system after severe injury.

The hypermetabolic low T_3 syndrome may occur in a variety of settings. Other types of trauma¹³ and several types of febrile illnesses¹⁴ are associated with hypermetabolism, and febrile illnesses are associated with elevated catecholamine excretion²⁹ and decreased T_3 levels.³⁰ Patients with extensive burns and probably patients with other nonthyroidal illnesses develop a hypermetabolic low T_3 syndrome. Their hypermetabolism is due, at least in part, to elevated catecholamine secretion. The syndrome in burn patients would appear potentially harmful in terms of extremely high levels of catecholamines or low levels of free thyroid hormones, but an attempt to alter it with T_3 administration did not greatly affect catecholamines, hypermetabolism, or mortality.

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